FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Arthritis Advisory Committee (AAC) Meeting
FDA White Oak Campus, Building 31, The Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
March 12, 2012

DRAFT Questions to the Committee

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1) **DISCUSSION:** The data presented today describe a safety signal seen in clinical studies of anti-nerve growth factor (anti-NGF) agents that are under development for the treatment of pain due to a variety of disorders. Please discuss whether these adverse events of painful, rapid joint destruction are occurring with an unusually high incidence in the populations studied and/or are unusually severe compared to joint-related events that occur in this population.

2) **DISCUSSION:** Do you agree with the sponsors' interpretation of the data which states that:

   a. Rapidly Progressing Osteoarthritis (OA) has been identified as a safety signal in the tanezumab and fulranumab clinical programs.

   b. Osteonecrosis does not represent a safety signal.

   c. Rapidly progressive osteoarthritis type 2 (Pfizer) is a relatively distinct finding in the tanezumab studies.

   d. Anti-NGF agents may represent an advantage in terms of efficacy over other analgesics for the treatment of OA and other painful conditions.

   e. The risk-benefit profile of tanezumab monotherapy in the treatment of OA is favorable compared to treatment with placebo, non-steroidal anti-inflammatory drugs (NSAIDS), or extended-release oxycodone.

   f. The risk-benefit profile of tanezumab/NSAID combination therapy is unfavorable compared to NSAID treatment alone and to tanezumab monotherapy.

   g. The data suggest that many events were pre-existing or associated with a subchondral insufficiency fracture of the knee or atrophic OA of the hip.

   h. NSAID use up to 90 days did not elevate risk.

   i. The data suggest that a possible mechanism for this safety signal is an increased load on a susceptible joint in the presence of pain relief.

3) **DISCUSSION:** Anti-NGF agents have been studied in a variety of conditions that represent very large populations, such as osteoarthritis and low back pain, with a number of approved therapies, and also in smaller populations that lack effective therapies, such as interstitial cystitis. Considering what is known thus far about the risks and benefit associated with this class of biologic agents, are there any populations for which further clinical development would be acceptable? If yes, discuss which specific patient populations/painful conditions may be appropriate for further study, as defined below.

a. **VOTE:** There are approved agents that have demonstrated efficacy in reducing pain intensity in conditions such as osteoarthritis. Based on the risks-benefit profile of these agents, is there a role for the ongoing development of the anti-NGF agents?

   i. DISCUSSION: Please discuss whether the anti NGF agents should be studied only in patients refractory to current standard of care.

b. **VOTE:** Is there a role for the ongoing development of anti-NGF agents to manage the pain associated with conditions for which there are no agents with demonstrated analgesic efficacy, such as interstitial cystitis or chronic pancreatitis?

   i. DISCUSSION: Please discuss whether the anti NGF agents should be studied only in patients refractory to other treatments.

4) If clinical trials are allowed to proceed:

   a. **DISCUSSION:** What screening procedures, safety monitoring and follow-up assessments should be included in the studies?

   b. **DISCUSSION:** Do the data support allowing clinical trials to proceed with some amount of concurrent NSAID use?

      i. **DISCUSSION:** If clinical trials study limited concurrent NSAID use, can NSAID use be limited post-approval?

   When answering the above questions, please refer to the sponsors' proposed safety measures outlined in the Agency's slide presentation.

5) **DISCUSSION:** Are there additional nonclinical studies that can be conducted that may provide additional insight into the possible etiologies for the bone and joint adverse events noted during the clinical development of these anti-NGF agents?